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Review

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Therapies in Inflammatory Bowel Disease Patients with Extraintestinal Manifestations

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Keywords
Extraintestinal manifestations · Crohn's disease · Ulcerative colitis · Inflammatory bowel disease · Infliximab · Ankylosing spondyloarthritis

Abstract
Extraintestinal manifestations (EIM) have become an important source of morbidity and disability as well as an identified risk factor for an unfavorably course of disease in inflammatory bowel diseases (IBD). Therefore, efforts have been put into a more global and interdisciplinary management of IBD patients in collaboration with rheumatologists, dermatologists, and ophthalmologists. A real therapeutic success has also been obtained with a more "systemic" IBD treatment associated with the development of monoclonal antibodies against TNF alpha and biological agents derived from the treatment of rheumatological disease (also called biological Disease-Modifying Antirheumatic Drugs). The prevalence of these EIM remains too low to undergo randomized controlled trials with this specific focus and therefore the evidence relies on case series and experts' opinions, which lowers the level of evidence. After a careful review of the most recent literature, this paper aims to update the reader on the latest therapeutic management of IBD patients with EIM.

Introduction

Extraintestinal manifestations (EIM) occur in about 50% of inflammatory bowel disease (IBD) patients over the course of their disease. The prevalence has initially been rather underestimated [1], but more recent cohorts reported on the increasing importance of this phenomenon [2].

The pathogenesis of the inflammation in IBD seems directly associated to it, as it acts beyond the gastrointestinal tract, making it a systemic disease. The most frequent EIM are distributed in 4 groups: musculoskeletal, ophthalmic, dermatological, and hepatobiliary disorders and could occur with or without a link to disease activity.

The development of EIM has a major impact on patient quality of life, increases the morbidity of these dis-

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Table 1. Characteristics of the most frequent EIMs

EIM	Parallel course of IBD	Separate course of IBD	May or may not parallel disease activity	Response to anti-TNF agents
Axial arthropathy		✓		+++
Peripheral arthropathy	✓ (Pauciarticular)	✓ (Polyarticular)		++
Erythema nodosum	✓			++
Pyoderma gangrenosum			✓	++
Oral aphtous ulcers	✓			++
Episcleritis	✓			++
Uveitis			✓	+++
Primary sclerosing cholangitis			✓	–

EIM, extraintestinal manifestation; IBD, inflammatory bowel diseases.

eases, and disability of IBD patients. This manifestation can occur before, at, or after the diagnosis of IBD and, if present, should, in the presence of highly suggestive EIM, motivate the search for an underlying IBD, thereby reducing the diagnostic delay. This has been nicely shown in the prospective Swiss IBD cohort study where about one-fourth of patients had EIM symptoms before IBD diagnosis was made [3].

Consequently, the caregivers have to take the patients with these manifestations more globally into consideration when deciding on a specific treatment and seek for the help of a multidisciplinary management including, among others: rheumatologists, dermatologists, and ophthalmologists. In the specific group of primary sclerosing cholangitis (PSC) patients, a life-threatening risk is present due to a much higher risk of development of neoplasia.

This review details the classification of the most common EIM, their characteristics, and treatment (Table 1). Extraintestinal complications of IBD, such as anemia, vitamin deficiency, or urolithiasis and associated diseases, are beyond the scope of this review.

Rheumatological and Musculoskeletal Manifestations

Articular manifestation affects approximately 30% of patients with patients with IBD, more Crohn's disease (CD) than ulcerative colitis (UC) [2, 4]. Peripheral joint pain is the most common EIM in patients with IBD; they are mostly noninflammatory and thus not comparable to inflammatory joint manifestations, which usually do not follow the course of disease and run independently [5]. IBD-associated axial arthritis is considered as a subgroup of the spondylarthropathies (SpA) by rheumatologists [6]. Interestingly, on the other hand, approximately 75% of patients with rheumatological disease will eventually develop digestives symptoms and even gut inflammation, but only about 7% will end up with an diagnosis of IBD [7] which is then considered as "extra-articular manifestation" [8]. However, it is also possible that the real prevalence of coexistence of IBD and EIM is underestimated in some patients who develop initially an EIM and are treated with biologicals that could mask the digestive involvement. The pathophysiological concept of the gut-joint axis is advocated to underlie these manifestations. Indeed, genetic studies highly suggest a link with genes, which may be implied in both disease phenomenon [9–12] and, that is, some receptors influencing bacterial impact on the gut and joints inflammation, such as scavenger receptor CD 163 on the macrophages surface, could also play a role [13, 14]. The idea of an aberrant homing of mucosal T cells and extraintestinal manifestations of IBD [15] has been also recently hypothesized in an interesting publication from Dubinsky et al. [16] to explain the link between an obvious higher rate of EIM and the use of vedolizumab in UC. The authors hypothesized that the natural homing of active lymphocytes, which migrate from the blood into the lymphoid tissues, regulated by adhesion molecules and chemokines, is voluntarily impaired (basic mechanism of the drug). By that mean, more activated lymphocytes remain in the circulation, traffic to other organ system and probably aberrantly bind to inflamed synovial vessels. This aberrant homing to the joints does not depend on a4b7-MAdCAM-1 interactions; however, several other adhesion molecules result (e.g., VAP-1) could act [17].

Table 2. Classification of enteropathic peripheral arthropathy associated with IBD. Adapted by S. Vavricka from the original article from [195]

Definition	Type I (pauci-articular)	Type II (polyarticular)
Prevalence CD, UC	6%, 3.6%	4%, 2.5%
Involvement	Asymmetric, <5 joints	Can be symmetric or asymmetric, may be erosive, 5 or more joints
Location	Mainly large joints: knee > ankle > wrist > elbow > MCP > hip > shoulder	Mainly small joints: MCP > knees >> PIP > wrist > ankle > elbow > shoulder
Parallels disease activity	Yes, similar to a reactive arthritis (e.g., post dysenteric)	No clinical course independent of IBD activity could predated the diagnosis of IBD
Natural course	Self-limited episodes that last <10 weeks	Persistent inflammation for months or even years
Associated	With HLA-B27, B35, and HLA-DR 103 with high frequency of EN and uveitis.	With HLA-B44 with uveitis

IBD, inflammatory bowel diseases; CD, Crohn's disease; UC, ulcerative colitis; MCP, metacarpophalangeal joint; PIP, proximal interphalangeal joints; HLA, human leukocyte antigen; EN, erythema nodosum.

IBD-Associated Axial and Peripheral Arthropathies

Peripheral arthropathies are described in the IBD literature as 2 types (1 and 2) [18] of which distinct characteristics and behaviors presented in Table 2. IBD axial arthropathy is considered as a subgroup of SpA, which are a chronic inflammatory disease of the axial skeleton and/or peripheral joints and also include ankylosing spondylitis (AS), psoriatic arthritis, reactive arthritis, and undifferentiated SpA. Axial SpA occurs in 4–10% of CD patients, and making these diagnoses based on inflammatory back pain is a challenge for the gastroenterologist. A recent publication and review of >250 patients from the Netherland conclude to an interesting and relevant referral algorithm for suspected axial spondyloarthritis in IBD patients. First, perform an anterior-posterior X-ray to search for a sacroiliitis (could be MRI in young patients to minimize radiation and make earlier diagnosis), when positive refer the patient. However, when negative, check for other SpA features such as inflammatory back pain, enthesitis, dactylitis, uveitis, positive family history, IBD, alternating buttock pain, psoriasis, arthritis, good response to nonsteroidal anti-inflammatory drugs (NSAID), elevated ESR/CRP, and perform an HLA-B27 serology. If ≥4 SpA features or 2–3 with positive HLA B-27, then referred (high probability of having axial SpA). Finally, patients with a positive HLA-B27 test and the presence of ≤1 SpA feature should undergo MRI [19]. This practical procedure is very close to the Assessment of SpondyloArthritis International Society criteria use for the diagnosis, summarized in Table 3.

Treatment of Arthropathies with Conventional Disease-Modifying Antirheumatic Drugs and Anti-TNF Alpha Agents (Biological Disease-Modifying Antirheumatic Drugs)

Patients with IBD-associated SpA are commonly treated with physical therapy and NSAIDs to relieve pain, swelling, and stiffness. Frequently used with success by rheumatologists, NSAIDs represent a very controversial option for IBD patients [20, 21] as that they have been accused of inducing increased rate of flares, hospitalization, and complications [22, 23], which are not found in a recent meta-analysis [24]. Therefore, NSAIDS should be used in the short term [25], or COX-2 inhibitors are an alternative option, as less negative data exist [26, 27], or paracetamol in case of residual pain or only minimal inflammation. Glucocorticoid injections directed to the local site of musculoskeletal inflammation may also be considered. Patients with axial disease should not receive long-term treatment with systemic glucocorticoids, as stated in the European League Against Rheumatism recommendations [25, 28]. Alternative drugs for resistant peripheral arthritis only are the Disease-Modifying Antirheumatic Drugs (DMARD) sulfasalazine and methotrexate. The use of these old drugs is mostly based on the recommendation for the treatment of AS [28]. The antimetabolite drug, methotrexate, is rather used in CD patients due to strongest evidence for the bowel disease and preferably for the indication of maintenance of a drug-induced remission or in combination with biologics [29].

Table 3. Inflammatory back pain criteria sets and mnemonic for assessment of axial spondyloarthritis, according to ASAS. Adapted from [196]

In patients with back pain ≥3 months and age at onset back pain <45 years (with/without peripheral manifestations)	
(1) Sacroiliitis on imaging – Active (acute) inflammation on MRI highly suggestive of sacroliitis associated with SpA – Definite radiographis sacroiliitis according to modified New York criteria	One or more SpA feature(s) – Inflammatory back pain – Arthritis – Enthesitis – Uveitis – Dactylitis – Psoriasis – CD/UC – Good response to NSAIDS – Family history for SpA
OR	
(2) HLA-B27 positivity	Two or more SpA feature(s) – HLA-B27 – Elevated CRP

SpA, spondyloarthritis; ASAS, Assessment of SpondylArthritis international Society; NSAIDS, nonsteroidal anti-inflammatory drugs; CRP, C-reactive protein; CD, Crohn's disease; UC, ulcerative colitis.

Finally, biological agents are, for now >20 years, the most efficient class of drugs to control all these rheumatologically manifestations, demonstrated in randomized clinical trials [30] as well as historical cases series [31, 32]. The indication of the most commonly used anti-TNF agents, infliximab [33] and adalimumab [34, 35], is multiple, and the efficacy reach a good level and also drives a high number of indications in IBD patients, as demonstrated recently in the Swiss IBD cohort study [36]. Paradoxal articular manifestations are also frequently described in IBD patients under anti-TNF treatment and do not warrant the need of discontinuation of the medication [37]. Golimumab [38, 39] and Certolizumab [40] are also other TNF inhibitors to consider when treating rheumatological EIM, in particular after a loss of response to infliximab due to autoimmunity (antibodies against the drug) [41, 42]. Finally, Vedolizumab, a gut-specific anti-integrin inhibitor, that blocks leucocytes migration to the inflammation site seems to influence mostly arthropathies linked to disease activity (Type II) in about 40% of the patients according to a small prospective French study [43], but also incidental inflammatory arthralgia/arthritis has been described in 14%, similarly to the publication from Mount Sinai Hospital [16]. The theoretical hypothesis of the authors of the latter study is that Vedolizumab administration may lead to the trafficking of α4β7-expressing lymphocytes to other organ systems and may predispose patients to develop EIMs with a parallel course to IBD.

Treatment of Arthropathies with Future IBD Therapies

Based on European League Against Rheumatism recommendations [28], biological DMARDs should be considered in patients with persistently high disease activity despite conventional treatment. Current practice is to start with TNF alpha therapy; however, most of IBD patients will eventually fail anti-TNF alpha agents due to either gastroenterological or rheumatological source of activity. That leads to the assumption that small molecules, acting as targeted DMARDs, such as tofacitinib or other more specific medication like JAK 1 inhibitors (upadacitinib, folgitinib, baricitinib, peficitinib) will be used probably early in the disease course of these IBD patients with EIM [44]. Of note, Apremilast (Otezla®), which phase III trial was not conducted in UC, as well as ustekinumab (Stelara®), which should soon have indication in IBD, did not demonstrate efficacy in rheumatoid arthritis. Data are also disappointing in SpA patients treated with ustekinumab. Therefore, small molecules such as apremilast and kinase inhibitors are clearly entering the field as potential new treatment options. A detailed overview is presented in Table 4 (with their references) and commented below.

Tofacitinib, a pan-JAK inhibitor in doses of 5 and 10 mg twice daily, has also been evaluated in phase II trials for clinical efficacy in patients with AS with promising results [45]; however, no further trials are planned for this

Table 4. Current stand of JAK inhibitors (and other small molecules), IL-6, IL-12, IL-17 inhibitors tested in rheumatological diseases and IBD

Name	Molecule	CD	UC	Rheumatoid arthritis	Ankylosing spondylitis	Psoriasis/PsA
Tofacitinib (1st gen.) CP690550	Pan-JAK inhibitor	☹ Pilot, phase IIb study [136, 137] ✓ Real life data ✓ OLE study [138] ✓ Objective inflammation [139]	Approved 2018 (Xeljanz®) [140, 141]	Approved 2012 [142] as efficient as adalimumab [142]	✓Phase IIb study [45] but than discontinued	Approved for PsA, but not psoriasis [143, 144]
Upadacitinib (2nd gen.) ABT-494	JAK1 selective inihibitor	✓ Phase IIb study [145] ✓ Effect on EIM [46] Ongoing phase III	✓ Phase IIb study [146, 147] Ongoing phase III	✓ Phase III [148]	No studies	No studies
Folgitinib (2nd gen.) GLPG0634	JAK1 selective inihibitor [149]	✓ Phase IIb study [150] Ongoing phase III	Ongoing phase III	✓ Phase III = FINCH 3 study	✓ Phase II	✓ Phase II
Baricitinib (1st gen.) INCB-28050/ LY-3009104	JAK1/JAK2 selective inihibitor	No studies	No studies	Approved 2017 (Olumiant®) [151, 152]	No studies	✓ Phase IIb [153] only for PsA
Peficitinib (1st gen.) GLPG1205 ASP-015K, JNJ-54781532	JAK3 selective inhibitor	No studies	☹ Phase IIb [154]	✓ Phase III [155]	No studies	discontinued
Apremilast NCT02289417	Phosphodiesterase 4 – inhibitor	No studies	✓ II [156, 157]/ will not undergo phase III	☹ Phase II [158]	✓ Phase II [159] ✓ Subgroup of phase III [160]	Approved 2014 (Otezla®) [161–163]
Tocilizumab	Anti-IL-6 receptor	✓ Pilot study [164]	☹ 1 case report of exacerbation [165] 1 case of improvement [166]	✓ Approved 2010 (Actemra®) [167] Higher risk of intestinal perforation [168]	☹ Phase II–III [169]	No studies
Ustekinumab NCT02407236	Anti-IL 23/12 (p40 Inhibitor)	✓ Approved 2016 (Stelara®) [170]	✓ Phase III	☹ Phase II [171]	☹ Phase III	✓ Approved 2013 for PsA [172, 173] 2009 for Psoriasis [174, 175] (Stelara®)
Briakinumab ABT-874 NTC00570986	Anti-IL 23/12 (p40 inhibitor)	✓ Phase IIb [176]	No studies	No studies	No studies	✓ Phase III [177] But withdrawal of FDA application due to severe adverse events.
Risankizumab ABBV 066, BI 6555066	Anti-IL 23 (p19 Inhibitor)	✓ Phase II [178] ongoing phase III	Ongoing phase III	No studies	☹ Phase II [50]	✓ Approved 2019 for Psoriasis (Skyrizi®) [179] ✓ Phase II for PsA [180]
Brazikumab MEDI2070/AMG-139	Anti-IL 23 (p19 Inhibitor)	✓ Phase IIa [181]	No studies	No studies	No studies	No studies
Guselkumab CNTO1959	Anti-IL 23 (p19 Inhibitor)	Ongoing phases II/III (galaxi)	Ongoing phases II/III	☹ Phase II [171]	✓ Phase II	✓ Approved 2017 for psoriasis (Tremfya®) [182, 183] ✓ Phase II for PsA [184]
Mirikizumab LY3074828	Anti-IL 23 (p19 inhibitor)	✓ Phase II [185]	✓ Phase II [186, 187]	No studies	No studies	✓ Phase II [188]
Brodalumab AMG 827/KHK4827	Anti-IL-17 RA	☹☹☹ Worsen, phase IIa [189]	No studies	No studies (phase II canceled)	✓ Phase III [190]	✓ Approved 2017 (Siliq®, Kyntheum®) [191]
Secukinumab AIN457, KB03303A	Anti-IL-17 A	☹☹☹ Worsen, phase IIa [49]	No studies	✓ Phase III [192]	✓ Approved 2016 (Cosentyx®) [193]	✓ Approved 2015 (Cosentyx®) [194]

IL, interleukin; IBD, inflammatory bowel disease; CD, Crohn's disease; UC, ulcerative colitis; PsA, psoriatic Arthritis.

additional indication. Similarly, baricitinib and ruxolitinib, which have a very similar spectrum of cytokine blockade to that of tofacitinib, have not been tested in IBD patients but probably have clinical potential. On reason could be the emergence of a "second generation" of JAK inhibitors for the treatment of immune-mediated diseases that exert a selective blockade of JAK1 or JAK3 which, in theory, should have less risk of hematopoietic toxicity, an effect largely secondary to JAK2 inhibition. Promising data have been recently presented at the European Crohn's and Colitis Organization congress in 220 upadacitinib-treated CD patients showing a resolution of >50% of the EIM with appropriate dosage of the drug compared to about 30% under placebo [46].

Biologics targeting interleukin (IL)-17 signaling have been approved for clinical use in AS. However, this mode of inhibition has demonstrated a deleterious effect with increased activity in CD patients in a phase III trial using secukinumab against placebo [47]. As plausible explanation, a major alteration of intestinal barrier function associated with IL-17 inhibition and dysbiosis have been demonstrated in Mouse models [48, 49]. Targeting specifically the IL-23/12 pathway seems also quite disappointing, as the anti-IL-23 biologic, risankizumab, failed to meet its primary endpoint in terms of efficacy in SpA [50] and ustekinumab, with a brighter spectrum, did not show enough efficacy in a phase III study in rheumatoid diseases [51]. Fingolimod and other, more selective, S1PR modulators are being developed for clinical use in IBD, but have, to our knowledge, not been tested in rheumatoid diseases.

Dermatological Manifestations

Up to 15% of IBD patients present with cutaneous EIM [2, 52]. These complications are usually diagnosed after excluding other skin disorders.

Erythema Nodosum

The frequency of erythema nodosum associated to IBD can reach up to 15% of CD and 10% of UC in some studies [52–54]. Erythema nodosum often coexists with eye and joint involvement, isolated colonic disease, and pyoderma gangrenosum. It presents with subcutaneous nodules, which are raised, tender, and red/violet and are typically located on the anterior part of the lower extremities. Rarely other body parts are involved [52]. Erythema nodosum is often self-limiting, and it depends on the activity of the underlying disease [55].

In mild cases, topical corticosteroids, use of analgesics, compression stockings, and leg elevations were used [56]. Severe disease courses are treated with systemic corticosteroids, immunosuppressive therapies, or TNF antibodies [57–61].

Pyoderma Gangrenosum

Pyoderma gangrenosum is a cutaneous EIM, which is more common in UC than in CD and affects women more frequently than men [61, 62]. Pyoderma gangrenosum often coexists with a familial history of UC, in patients with pancolitis, permanent stoma, eye involvement, and erythema nodosum, and it is more prevalent in African-Americans [54]. The prevalence of pyoderma gangrenosum in IBD is 0.4–2% [1, 2, 53, 63, 64]. Most pyoderma gangrenosum lesions occur after a trauma (even years later), a phenomenon, which is known as pathergy. The lesions start as a small pustule, which spreads rapidly and develops deep purulent ulcers [65]. They mostly occur on extensor surfaces of the legs (shins) and adjacent to a postsurgical stoma, but can occur anywhere on the body, including the genitalia [66]. Pyoderma gangrenosum may improve if the underlying IBD is treated successfully. Mild cases usually respond to local and topical therapy. Unusually, intralesional corticosteroid injections, moist treatment with hydroactive dressings, and topical sodium cromoglycate are used [65, 67]. In more severe cases, systemic therapies such as oral sulfasalazine, dapsone, corticosteroids, and immunomodulators (azathioprine, cyclophosphamide, cyclosporine, methotrexate, tacrolimus, and mycophenolate mofetil) are used [56, 65, 68, 69]. TNF-antibody therapy has show good therapeutic results in several case series and case reports for infliximab [70–76] and for Adalimumab [77, 78]. A success rate comparable to therapy of luminal IBD (>60%) has been described in cases series of PG treated with Infliximab [70–76], but mostly linked to publication bias. For an overview on TNF-antibody therapies in EIM, please see reference [79].

Sweet Syndrome

Sweet syndrome, or acute febrile neutrophilic dermatosis, is a rare dermatologic manifestation associated with CD and UC [80, 81]. Sweet syndrome is not only associated with IBD but also can occur in other systemic diseases and malignancies. Sweet's syndrome manifests as tender or papulosquamous exanthema or nodules involving the arm, legs, trunk, hands, or face. Laboratory and histological features of Sweet's syndrome are leukocytosis and a neutrophilic infiltrate. Patients present usually with

arthritis, fever, and ocular symptoms, mainly conjunctivitis. Its association with IBD usually parallels the gastrointestinal disease activity but may precede the diagnosis of IBD [82]. IBD patients with Sweet's syndrome respond to topical or systemic corticosteroid therapy [83] and heal without scarring. Metronidazole has been reported to be effective in one case report [82].

Oral Aphthous Lesions

Mainly in CD patients, the oral cavity of IBD patients can be affected. Besides periodontitis, aphthous lesions can occur. In severe cases, this is called pyostomatitis vegetans [2, 84–86]. Oral aphthous lesions usually follow the course of the underlying IBD. Aphthous lesions are typically located on the labial and buccal mucosa but may also affect the tongue and oropharynx. Pyostomatitis vegetans manifests as multiple pustular sometimes hemorrhagic eruptions anywhere on the oral mucosa with a cobblestone pattern. Antiseptic mouthwashes and topical steroids are used as therapy [56, 87].

Hepatological Manifestations

Steatosis and other Frequent Liver Diseases

The most frequent (1.5–55%) hepatic extraintestinal complications of IBD patients are the nonalcoholic fatty liver disease (from steatosis to nonalcoholic steato-hepatitis, or even cirrhosis) [88, 89]. A recent large screening study of IBD patients from Canada detected nonalcoholic fatty liver disease in 33% of them, with 12% fibrosis [90]. Therefore, clinicians should be vigilant in screening patients with IBD for these diseases, as well as for cholecystolithiasis. A disturbed metabolism in IBD patients is causing these diseases to occur in concordance with rapid and large weight changes and steroid use. The prevalence of all liver disease in IBD is probably around 20% [91], among them drug-induced liver disease, vein thrombosis of the hepatic or portal, liver amyloidosis, and granulomatous hepatitis. Autoimmune hepatitis occurs also more frequently in IBD patients, associated with IBD diseases or with PSC.

Primary Sclerozing Cholangitis

PSC is a rare cholestatic liver disease characterized by progressive fibroinflammatory destruction of the intra- and/or extrahepatic biliary ducts of unknown origin [92].

Its diagnosis is based on a combination of typical symptoms and elevated serum markers of cholestasis (AP, γGT) not otherwise explained, characteristic bile duct changes in MRCP (or ERCP), and histological features (if required due to a normal cholangiogram).

More than 70% of PSC patients have IBD (75% UC) in European population, whereas the opposite is only around 1–3% (5% for UC). This explains the European guidelines suggesting an endoscopy at diagnosis of PSC and then every 3–5 years [93]. This diseases' association established since the sixties [94] exhibits a very specific IBD phenotype: a mildly active pancolitis with a right-to-left inflammatory gradient associated with a greater incidence of backwash ileitis and rectal sparing [95]. The evolution of the liver disease is completely asymptomatic and can only be detected when the persistence of abnormal cholestatic pattern of the liver tests is further investigated with MRCP [96] and liver biopsy (for small-duct PSC) [25].

The hallmark of PSC associated with IBD is the higher risk of developing cancers and for 50% of them it will be the cause of death, in order of frequency and risks [97]: cholangiocarcinoma (161×) [98], pancreas (14×), colorectal carcinoma (11×), gallbladder, and hepatocellular carcinoma. These data are based on a cohort study from Sweden [99, 100], which had included 604 PSC patients from 10 hospital between 1970 and 1998, and the colorectal cancer risk assessed by a meta-analysis [101] has also been confirmed by a French study [102] with 75 PSC-IBD patients during a >40-year follow-up (1963–2006). Whereas colorectal cancer and gallbladder cancer [103], colonoscopy, ideally with chromoendoscopy, and ultrasound are recommended annually [25, 93, 104, 105], for cholangiocarcinoma annual surveillance using imaging (MRCP or US in a 12–24 month interval) and CA 19–9 is now being suggested [25, 105, 106] but has not reach the level of international recommendations and must therefore be considered with caution. For other hepatic cancer recent data from the Mayo clinic demonstrated also an impact of screening with imaging modalities [107].

As no efficient treatment exists and the course of disease is unpredictable, liver transplantation remains the final treatment of PSC-induced end-stage disease or hepatocarcinoma. Unfortunately, the disease will eventually recurs on the graft (about 20% at 5 years). The controversy concerning the ursodeoxycholic acid based on a placebo-controlled trial published in 1997 showing no survival benefit [108, 109] is not solved by the international recommendations: the American association recommends against it [110], whereas the European association let it open to the discretion of the physician [25, 111]. In real practice, most experts suggest a dosage of 15 mg/kg [106]. There is a need for a better understanding of the

mechanistical cause, and new more relevant clinical endpoints are [112] for incoming studies on new agents. One part of the solution could potentially come through the modulation of the microbiome and or bile acids, as it is now considered as part of the etiopathogenesis of this disease [113, 114]. In example, oral vancomycin has been tested in a small cohort of children with a substantial benefit; however, a long-term use remains questionable [105]. The finding of aberrant expression of gut-restricted receptors for the adhesion molecule, such as α4β7, within the liver leads to a new hope when using the α4β7 monoclonal antibody, vedolizumab. The most recent data with an only 12-month follow-up showed only a slight impact on PSC-IBD. However, the lack of long-term follow-up endpoints such as end-stage liver disease, transplantation, and mortality could not be assessed [114].

Associated symptoms, such as pruritus, fatigue, and metabolic bone disease linked to PSC, need to be adequately managed by the physician. Cholestyramine (4 g once or twice daily) should be started and, if unsuccessful, rifampicin, sertraline, and naltrexone are good alternatives. Calcium and vitamin D intake should be optimized and associated with enough physical exercise. Bone densitometry should be performed every 2–3 years and in cases of significant finding (osteopenia/porosis) an appropriate bisphosphonate treatment initiated. Advanced stage disease leads to recurrent bacterial cholangitis as well as additional burden of a secondary biliary cirrhosis. Endoscopic treatments have some relevance has recently summarized in European Guidelines with balloon dilation rather than stents which induce more complications [25, 93]. However, the frequency of these interventions should be balanced with the risk of being iatrogenic.

Ophthalmological Manifestations

Up to 2–5% of patients with IBD suffer from ocular manifestations, which include episcleritis and uveitis [55, 84, 115]. CD patients present more often with ocular manifestations (3.5–6.3%) than UC patients (1.6–4.6%) [2, 52, 55, 115–117]. Patients aged over 40 years have more likely iritis/uveitis than those aged <40 years [118].

Episcleritis and Scleritis

Episcleritis is defined as a painless hyperemia of the conjunctiva and sclera. Episcleritis is not associated with changes of the visus. CD patients present more often with episcleritis than UC patients [119]. Since episcleritis often parallels the underlying IBD, it does not need a specific therapy other than treating the underlying IBD. Scleritis on the other hand affects the deeper layers of the eye. Patients present with severe ocular pain and tenderness to palpation [120]. Scleritis can cause changes of the visus. Early diagnosis is therefore pivotal. If not treated, severe complications such as scleromalacia, retinal detachment, or optic nerve swelling may occur. It is therefore mandatory to start early and aggressive therapy. Disease-specific treatment and topical steroid therapy usually provide prompt relief of symptoms. In case of impairment of vision, the presence of scleritis must be suspected, and prompt referral to an ophthalmologist is mandatory to avoid vision loss.

Uveitis

Uveitis is less common than episcleritis and occurs in 0.5–3% of patients with IBD. Anterior uveitis is the most common ocular manifestations of IBD. Uveitis is divided into 4 different manifestations: (i) anterior uveitis with a main site of inflammation in the anterior chamber, (ii) intermediate uveitis, where the inflammation is primary in the vitreous region, (iii) posterior uveitis, where retina and chorea are primarily involved, and (iv) panuveitis with its primary site of inflammation including anterior chamber, vitreous, retina, and choroid. The activity of uveitis is independent of the underlying IBD activity. Patients usually complain of pain and in case of iritis (anterior uveitis) of photophobia, red eye, blurred vision, and floaters (mooches volantes). A small number of treatment options in IBD patients suffering from uveitis have been published [121–128]. Prompt diagnosis and treatment with topical and systemic corticosteroids is necessary to prevent progression to blindness. Steroid refractory cases are treated with cyclosporine A. Successful use of infliximab for IBD-associated uveitis was demonstrated in a CD patient with uveitis and sacroiliitis [128].

Other Rare EIM

Other rare EIM of IBD have been described in the other organs. Their management is more disease specific and will not be detailed here. Neurological EIM are mostly peripheral neuropathy [129], whereas central demyelinating diseases have been shown as well [130]. Pulmonary involvement exists with reports involving different parts of the bronchial tree from the glottis to small airways. In particular, interstitial pneumonitis has been suggested 20–55% of IBD patients [131], the most frequent remaining drug induced (5-ASA compounds, methotrexate, or anti-TNF alpha agents) [132] and infections. IBD patients are at increased risk of cardiovascular events (mainly ve-

nous and arterial thromboembolism, myocardial infarction) which are more linked to the chronic inflammatory pattern of the disease and less to very rare associated cardiovascular diseases [25, 133]. Finally, pancreatitis associated with IBD could also be considered as EIM after inclusion of biliary pancreatitis, drug-induced (i.e., azathioprine, amino salicylates) or autoimmune cause [134, 135].

Discussion and Conclusion

In the present review, we illustrate an update on the management of EIM of IBD patients. Whereas no new effective treatments has been identified so far for treatment of PSC but a high importance of performing cancer surveillance, on the other hand, a bench of new molecules will emerge with an overlapping effect on gastrointestinal and rheumatological diseases. This later constellation is also linked to uveitis, which suggested that this EIM will probably also be improved by these therapies. The future is of the management of EIM remains bright and the understanding of their management is central to the gastroenterologist as it occurs in almost half of IBD patients and sometimes drives unilaterally treatment indication.

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Disclosure Statement

Authors declare no conflict of interest.

Author Contributions

P.J., J.Z., and S.R.V. reviewed the literature and prepared the draft of the manuscript. All co-authors reviewed the paper and improved its scientific and clinical content.

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